Polypharmacy and Kidney Function in Community-Dwelling Adults Age 60 Years and Older: A Prospective Observational Study

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Abstract: Objectives Information on the impact of polypharmacy on kidney function in older adults is limited. We prospectively investigated the association between intake of total number of drugs or nonsteroidal anti-inflammatory drugs (NSAIDs) and kidney function. Design Our study is a prospective observational analysis of the 2-year Zurich Multiple Endpoint Vitamin D Trial in Knee Osteoarthritis Patients. Setting and participants Of the 273 participants of the original trial, 270 participants (mean age 70.3 ± 6.4 years, 53% women) were included in this observational analysis. Methods The associations between (1) total number of drugs (or NSAIDs) at baseline or (2) cumulative number of drugs (or NASAIDs) repeatedly measured over 24 months and kidney function repeatedly measured over 24 months as estimated glomerular filtration rate (eGFR) were investigated using multivariable-adjusted repeated-measures analysis. Results Per drug at baseline, kidney function decreased by 0.64 mL/min/1.73 m2 eGFR (Beta = −0.64; 95% CI −1.19 to −0.08; P = .024) over 24 months. With every additional drug taken cumulatively over 24 months, kidney function decreased by 0.39 mL/min/1.73 m2 eGFR (Beta = −0.39; 95% CI −0.63 to −0.15; P = .002). In a high-risk subgroup, per NSAID taken cumulatively over 24 months, kidney function declined by 1.21 mL/min/1.73 m2 eGFR (Beta = −1.21; 95% CI −2.35 to −0.07; P = .021). Conclusions and implications For every additional drug prescribed among older adults, our study supports an independent and immediate harmful impact on kidney function. This negative impact seems to be about 3 times greater for NSAIDs compared with an additional average drug.

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Original Study

Polypharmacy and Kidney Function in Community-Dwelling Adults Age 60 Years and Older: A Prospective Observational Study

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A B S T R A C T

Objectives: Information on the impact of polypharmacy on kidney function in older adults is limited. We prospectively investigated the association between intake of total number of drugs or nonsteroidal anti-inflammatory drugs (NSAIDs) and kidney function.
Design: Our study is a prospective observational analysis of the 2-year Zurich Multiple Endpoint Vitamin D Trial in Knee Osteoarthritis Patients.
Setting and participants: Of the 273 participants of the original trial, 270 participants (mean age 70.3 ± 6.4 years, 53% women) were included in this observational analysis.
Methods: The associations between (1) total number of drugs (or NSAIDs) at baseline or (2) cumulative number of drugs (or NASAIDs) repeatedly measured over 24 months and kidney function repeatedly measured over 24 months as estimated glomerular filtration rate (eGFR) were investigated using multivariable-adjusted repeated-measures analysis.
Results: Per drug at baseline, kidney function decreased by 0.64 mL/min/1.73 m^2 eGFR (Beta = −0.64; 95% CI −1.19 to −0.08; $P = .024$) over 24 months. With every additional drug taken cumulatively over 24 months, kidney function decreased by 0.39 mL/min/1.73 m^2 eGFR (Beta = −0.39; 95% CI −0.63 to −0.15; $P = .002$). In a high-risk subgroup, per NSAID taken cumulatively over 24 months, kidney function declined by 1.21 mL/min/1.73 m^2 eGFR (Beta = −1.21; 95% CI −2.35 to −0.07; $P = .021$).
Conclusions and implications: For every additional drug prescribed among older adults, our study supports an independent and immediate harmful impact on kidney function. This negative impact seems to be about 3 times greater for NSAIDs compared with an additional average drug.

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The population segment of adults age 65 years and older is growing rapidly to an expected 30% in 2050.[1,2] Inevitably, this demographic change will be associated with an increase in the number of age-related chronic diseases treated with a rising number of drugs.[3] Polypharmacy among the growing segment of older patients raises concerns about limited data on how common drugs individually and in combination affect kidney function in older adults, as this segment of the population has been largely excluded from clinical trials.[4]

Notably, the percentage of adults aged 65 years or older taking 5 or more drugs has doubled from 20% in 1995 to almost 40% in 2010.[3] In the same time period, the incidence of chronic kidney disease (CKD) has also more than doubled in this age group.[5] Age alone will decrease the glomerular filtration rate (GFR) by about 0.8 to 1 mL/min/1.73 m^2/year over the age of 40 years.[6–8] And age-related chronic diseases such as hypertension,[9] diabetes,[10] and obesity[11] have been shown to negatively impact kidney function independent of age.[11]

In addition, several drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs),[12,13] virostatics,[14] calcineurin inhibitors,[15] and bisphosphonates,[14] have been identified as high-risk drugs, especially if kidney function is already impaired due to prevalent age-related chronic diseases.[16,17] However, although the association between reduced kidney function and the risk of mortality, cardiovascular events, and rate of hospitalization is well established,[18] only limited data is available on how polypharmacy affects kidney function prospectively and cumulatively among community-dwelling adults aged 60 years and older.[17]

Therefore, in this study, we investigated the association between polypharmacy and kidney function prospectively over 2 years with 6 monthly assessments among adults aged 60 years and older, both with regard to baseline and cumulative exposure over time. We also performed a subgroup analysis for NSAIDs as a known high-risk medication.

Methods

Participants and Study Design

The present study is a secondary observational analysis utilizing data that was originally collected as part of the Zurich Multiple Endpoint Vitamin D Trial in Knee Osteoarthritis Patients (NCT00599807),[19] a 2-year single-center double-blind randomized controlled trial (RCT) investigating the effect of vitamin D (2000 IU/d vs 800 IU/d cholecalciferol) on pain and disability in patients with knee osteoarthritis between 2008 and 2014 at the University Hospital Zurich, Switzerland.

The original RCT enrolled 273 participants aged 60 years and older (community-dwelling, mean age 70.4 years, 53% women) who were undergoing elective surgery for unilateral knee replacement because of severe knee osteoarthritis and were recruited from 2 large hospital centers (Schulthess Clinic, Zurich; Triemli City Hospital, Zurich).[19] Exclusion criteria of the original RCT important for the present study included history of inflammatory arthritis, chronic corticosteroid use, hypercalcemia, kidney disease (estimated creatinine clearance by Cockroft-Gault equation $<$30 mL/min), kidney stone within 10 years, and current cancer.

Throughout the original 2-year trial, participants were invited to the study center at baseline and every 6 months (at 6, 12, 18, and 24 months) for a follow-up visit. At each visit, drug intake was updated and kidney function parameters including serum creatinine (sCr), serum cystatin C (sCys), and urine albumin were measured. Of the 273 participants enrolled in the original RCT, 270 participants who had complete information on kidney function and medication intake at baseline were included in the present observational analysis. Of these 270 participants, data of 259 (96% at 6 months), 254 (94% at 12 months), 243 (90% at 18 months), and 226 (84% at 24 months) participants were available for the present observational analysis because of drop outs (n = 44) during the original RCT.[19]

The original RCT was in accordance with the principles as outlined in the Declaration of Helsinki of 1975 as revised in 1983, and all participants gave their written informed consent to the study, which was approved by the Cantonal Ethical Commission of Zurich (Protocol identifier STZ 20/07), Switzerland. The proposal for the present secondary investigation on the prospective association between polypharmacy and kidney function was approved by the Ethics Committee Zurich (ID 2016-00750).

Assessment of Drug Intake

Self-reported intake of prescribed and over-the-counter drugs was assessed at each visit (ie, at baseline and 6, 12, 18, and 24 months), including the brand name, Anatomical Therapeutic Chemical Classification (ATC) code,[20] ingredients, dose, dosage, indication, and duration. For the present analysis and to be consistent with the literature on polypharmacy,[21,22] we excluded drugs taken "as needed," all herbal medicines, homeopathics, and nutritional supplements. We included all types of drug applications (ie, oral, topical, nasal, inhaled, and parenteral).

For each participant, the self-reported total number of different drugs taken at each time point was counted. In addition, based on these numbers, for each participant the cumulative number of drugs taken at a specific visit was calculated as the sum of all drugs taken up to that visit. We used a cumulative concept of polypharmacy, defining it as the sum of all different types of drugs having a different ATC code and taken daily at baseline or within 1 of the four 6-month follow-up periods. For instance, if a participant took both paracetamol and pantoprazole daily, the cumulative intake at baseline was 2. If the participant continued with the same medication from baseline over the whole 24-month observational period, the cumulative intake was 10, which is the sum of 2 drugs counted for the baseline assessment and for each of the four 6-month periods (eg, baseline visit + 6 + 12 + 18 + 24-month visit). We did this based on the hypothesis that drug-related nephrotoxicity increases over time when the drug is not withdrawn. So, the cumulative calculation was performed to take the accumulated drug-related nephrotoxicity into account.

We used the ATC code to group individual drugs according to classes and subclasses of drugs.[20] The group of NSAIDs included acetic acid derivatives and related substances (ATC: $M01AB^0$) [ie, oxicams ($M01AC^0$), propionic acid derivatives ($M01AE^0$)], other anti-inflammatory and antirheumatic agents (nonsteroids) ($M01AX^0$), coxibs ($M01AH^0$), fenamates ($M01AG^0$), and salicylic acid and derivatives ($N02BA^0$), exclusive of chondroitinsulfat and glucosamine (M01AX25, M01AX05). Acetylsalicylic acid was only classified as NSAID when used as pain killer (500 mg), but not when used for cardiovascular disease prevention (100 mg).

Assessment of Participant Characteristics and Covariates

Age, sex, diabetes, hypertension, and Charlson comorbidity index (CCI, score 0–37)[23] were assessed by questionnaire at baseline. Weight (kg) and height (cm) were measured at baseline. Body mass index (BMI, in kg/m^2) was calculated as weight divided by height squared. Treatment of the original RCT compared an oral dose of 2000 IU to 800 IU vitamin D_3 per day. Additional assessment of prevalent and incident comorbidities, hospitalization, frailty criteria, and prevalence of frailty is described in the online Supplementary Material (Supplementary Table 1).

Table 1
Prospective Association Between Continuous Values of Baseline or Cumulative Drug Intake and Kidney Function Over 24 mo

Baseline or Cumulative Drug Intake	Overall Kidney Function (eGFR) over 24 Mo			
	Unadjusted Analysis *Beta* (95% CI)	*P*	Adjusted Analysis *Beta* (95% CI)	*P*
Total drugs				
At baseline	−2.37 (−3.24 to −1.49)	.001	−0.64 (−1.19 to −0.08)	.024
Cumulative over 24 mo	−0.84 (−1.16 to −0.52)	<.001	−0.39 (−0.63 to −0.15)	.002
NSAIDs, mean (SD)				
At baseline	−2.32 (−7.20 to 2.56)	.47	−1.97 (−4.51 to 0.59)	.26
Cumulative over 24 mo	−1.25 (−2.70 to 0.10)	.09	−1.21 (−2.35 to −0.07)	.021

Data (n = 270 at baseline, ie, 0 mo; n = 259 at 6 mo; n = 254 at 12 mo; n = 243 at 18 mo, n = 226 at 24 mo) are unstandardized regression coefficients (*Beta*) of multivariable linear repeated-measures models unadjusted or adjusted for age, sex, BMI, treatment groups of the original RCT, prevalence of diabetes, prevalence of hypertension, and the baseline value of the eGFR. Further adjustment for the CCI did not significantly change the results. Regression coefficients (Beta) indicate the impact of an additional drug taken at baseline or taken cumulatively over 24 mo on kidney function (measured as CKD-EPI$_{cr\text{-}cys}$ eGFR) (ie, after adjusting for covariates, an increase in drug intake at baseline or in drug intake taken cumulatively over 24 mo by 1 unit was associated with a change of *Beta* units in the eGFR). *P* values are 2-sided; statistical significance was set at $P < .05$.

Assessment of Kidney Function

We defined kidney function as the Chronic Kidney Disease Epidemiology Collaboration creatinine- and cystatin C-based estimated GFR (CKD-EPI$_{cr\text{-}cys}$ eGFR).[24,25] Different studies have suggested that the CKD-EPI$_{cr\text{-}cys}$ formula shows the most exact estimated GFR for older adults in the age range of our study.[7,24–26] The CKD-EPI$_{cr\text{-}cys}$ eGFR was calculated by using the age- and sex-related formula defined by Inker et al.[24] Fasting blood samples were taken in the morning when the participants arrived at the study center. sCys concentration was determined using a BN100 nephelometer (Dade Behring Inc, Deerfield, IL) particle-enhanced immunonepholometric assay[27] (inter-assay coefficient of variation of 5.9% at a level of 1.14 mg/L and 4.8% at a level of 2.18 mg/L). sCr concentration was determined using a kinetic Jaffe method traceable to isotope dilution mass spectrometry (IDMS) (Roche Diagnostics, Rotkreuz, Switzerland) with an inter-assay coefficient of variation of 2.4% at a level of 95 μmol/L and 2.3% at a level of 337 μmol/L. sCr, sCys, and CKD-EPI$_{cr\text{-}cys}$ eGFR were measured at each visit (ie, at baseline and 6, 12, 18, and 24 months using collected venous blood).

Statistical Analyses

Statistical analysis was performed using SAS v 9.4 (SAS Institute, Inc, Cary, NC). Differences in baseline characteristics between men and women were analyzed using a χ^2 test for categorical variables and Student *t*-test for continuous variables. *P* value for trend across tertiles of drug intake was calculated from linear regression models using the median value of the individual tertiles as a continuous variable. We analyzed the number of drugs as continuous variables and tertiles because there is no consensus for the polypharmacy definition, particularly in multimorbid older adults.[28]

As the primary observational analysis, we analyzed the association of (1) the total number of drugs (as continuous predictor variable) at baseline or (2) the cumulative intake of drugs (as continuous predictor variable) at 6, 12, 18, or 24 months with repeated measurements of kidney function (as continuous response variable) at 6, 12, 18, and 24 months using multivariable-adjusted linear repeated-measures models with compound-symmetry covariance structure. To account for possible confounders that may bias the association between drug intake and kidney function over time because they may also influence kidney function, we adjusted our analysis for age, sex, BMI, treatment groups of the original RCT, prevalence of diabetes, prevalence of hypertension, and the baseline value of the eGFR. To account for the prevalence of further comorbidities (besides diabetes and hypertension), we additionally adjusted our models for the baseline CCI, however, this adjustment did not statistically significantly or meaningfully change the results.

Generally, the "*Beta*" values (unstandardized regression coefficients of the multivariable-adjusted models) stated for the predictor variables (1) baseline or (2) cumulative drug intake in the results section and Table 1 indicate the impact of an additional drug taken at baseline or taken cumulatively over 24 months on kidney function (measured as CKD-EPI$_{cr\text{-}cys}$ eGFR [mL/min/1.73 m^2]) after adjusting for confounding covariates [ie, an increase in drug intake at baseline or in drug intake taken cumulatively over 24 months by 1 unit (ie, 1 drug) was associated with a change in the eGFR by the numerical value of "*Beta*" units (ie, mL/min/1.73 m^2)].

For subgroup analysis on the association between the number of NSAIDs (as a continuous predictor variable) taken at baseline or the cumulative number of NSAIDs (as continuous predictor variable) taken up to the 6-, 12-, 18-, and 24-month follow-up and kidney function (as continuous response variable) at the 6-, 12-, 18-, and 24-month follow-up, we used the same multivariable-adjusted linear repeated-measures models as in the primary analysis.

In addition, we performed a sensitivity analysis to assess the association between total number of drug intake (as a continuous predictor variable) and kidney function (as continuous response variable) with and without adjusting for the number of RAAS blockers (ie, angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers) in the multivariable-adjusted model of the primary analysis to account for a possibly biased eGFR reduction through the mode of action of RAAS blockers, which preserve renal function by lowering intraglomerular pressure, thereby resulting in a reduction in GFR.[29]

Statistical significance was set at *P* value of $\leq .05$, and reported *P* values are 2-sided.

Results

Participant Characteristics

Among the 270 participants included in the present analysis [mean age 70.3 ± 6.4 years, 53% women, BMI 27.9 ± 4.5 kg/m^2, mean CCI 0.5 ± 0.9 (score 0–37); Table 2], the mean intake of drugs at baseline and the cumulative intake of drugs over 24 months were 2.4 ± 2.2 and 14.5 ± 10.5 drugs, respectively. The mean intake of NSAIDs at baseline and the cumulative intake of NSAIDs over 24 months were 0.17 ± 0.4 and 0.71 ± 1.4 NSAIDs, respectively. The mean eGFR of the total study sample was 81.6 ± 15.1 mL/min/1.73 m^2. Categorized by the "Kidney Disease: Improving Global Outcomes" (KDIGO) classification (Supplementary Figure 1), participants in the KDIGO GFR G1 (eGFR ≥90), GFR G2 (eGFR 60–89), GFR G3a (eGFR 45–59), and GFR G3b (eGFR 30–44) category had mean intakes of 1.92, 2.48, 3.80, and 4.80 drugs at baseline, respectively. Additional information on prevalent and incident comorbidities, hospitalization, frailty criteria, and prevalence of frailty of the participants (Supplementary Table 1) indicates that besides hypertension, diabetes, and cardiovascular disease, both

Table 2
Participant Characteristics by Sex

	Men	Women	Sex Difference (*P*)	Total Population
Participants, n (%)	126 (46.7)	144 (55.3)	.25	270
Age, mean (SD), y	70.3 (6.9)	70.2 (6.0)	.98	70.3 (6.4)
Body mass index, mean (SD), kg/m^2	28.4 (4.7)	27.4 (4.3)	.07	27.9 (4.5)
Prevalent hypertension, n (%)	64 (51.5)	58 (41.3)	.09	122 (46.0)
Prevalent diabetes, n (%)	10 (7.9)	6 (4.2)	.21	16 (6.0)
CCI (score 0–37), n (%)	0.6 (1.0)	0.4 (0.9)	.06	0.5 (0.9)
<3	108 (85.7)	125 (89.9)	.29	233 (87.9)
≥3	18 (14.3)	14 (10.1)		32 (12.1)
Intake of drugs (average number)				
Total drugs				
At baseline, mean (SD)	2.40 (2.18)	2.48 (1.89)	.76	2.4 (2.0)
Cumulative at 24 mo, mean (SD)	14.80 (11.54)	14.52 (9.67)	.84	14.7 (10.6)
NSAIDs, mean (SD)				
At baseline, mean (SD)	0.14 (0.33)	0.19 (0.43)	.35	0.17 (0.39)
Cumulative at 24 mo, mean (SD)	0.68 (1.21)	0.75 (1.47)	.73	0.71 (1.35)
CKD-EPI$_{cr\text{-}cys}$ eGFR, mean (SD), mL/min/1.73 m^2	81.9 (15.8)	81.4 (14.4)	.78	81.6 (15.1)

Data (n = 270 at baseline and n = 226 at 24 mo) are crude means (±SD) or n (%). Differences between men and women were assessed by using Student *t* test for continuous variables and a χ^2 test for categorical variables. *P* values are 2-sided; statistical significance was set at $P < .05$.

the prevalence of other comorbidities at baseline and the incident comorbidities and hospitalization over time, as well as the prevalence of frailty over time, were low in our study population.

Stratified by sex (Table 2), men had a higher BMI and a higher CCI than women, however, these differences only approached statistical significance. Stratified by tertiles of total drug intake at baseline (Table 3), mean age, BMI, CCI, and frequency of prevalent hypertension and diabetes increased significantly across drug intake tertiles, whereas eGFR decreased significantly.

Prospective Association Between Intake of Drugs and Kidney Function

In the primary analysis (Table 1), over 24 months, with every additional drug taken at baseline, kidney function declined by 0.64 mL/min/1.73 m^2 eGFR in adjusted (*Beta* = −0.64; $P = .024$) and unadjusted (*Beta* = −2.37; $P < .001$) analysis. Also, with every additional drug taken cumulatively over 24 months, kidney function decreased by 0.39 mL/min/1.73 m^2 eGFR in adjusted (*Beta* = −0.39; $P = .002$) and unadjusted (*Beta* = −0.84; $P < .001$) analysis (Table 1).

Subgroup Analysis on NSAID Intake and Kidney Function

Regarding the intake of NSAIDs (Table 1), there was no significant association between the number of NSAIDs at baseline and the decline in kidney function over 24 months in adjusted (*Beta* = −1.97; $P = .26$) and unadjusted (*Beta* = −2.32; $P = .47$) analysis. However, with every additional NSAID taken cumulatively over 24 months, kidney function declined by 1.21 mL/min/1.73 m^2 eGFR in adjusted (*Beta* = −1.21; $P = .021$) and nonsignificantly in unadjusted (*Beta* = −1.25; $P = .09$) analysis (Table 1).

Sensitivity Analysis

When additionally adjusting the association between the baseline or cumulative total number of drugs and kidney function for RAAS blockers, over 24 months, higher baseline (*Beta* = −0.63; 95% CI −1.20 to −0.06; $P = .030$) or cumulative (*Beta* = −0.38; 95% CI −0.62 to −0.14; $P = .002$) intake of drugs was not associated with a significantly smaller decline of kidney function than without adjusting for

Table 3
Participant Characteristics by Tertiles of Total Drug Intake at Baseline

	Tertile 1 (0–1 Drugs)	Tertile 2 (2–3 Drugs)	Tertile 3 (4–10 Drugs)	*P* or P_{trend}
Participants, n (%)	101 (37.0)	102 (37.4)	70 (25.6)	<.001
Female, n (%)	54 (37.5)	52 (35.1)	38 (26.4)	.81
Age, mean (SD), y	69.1 (6.7)	70.3 (6.2)	71.8 (6.0)	.008
Body mass index, mean (SD), kg/m^2	27.2 (4.1)	27.8 (4.9)	29.0 (4.3)	.020
Prevalent hypertension, n (%)	16 (16.3)	53 (53.0)	53 (79.1)	<.001
Prevalent diabetes, n (%)	1 (1.0)	3 (3.0)	12 (17.7)	<.001
CCI (score 0–37), n (%)	0.32 (0.68)	0.37 (0.82)	0.97 (1.24)	<.001
<3	90 (91.8)	92 (92.0)	51 (76.1)	.003
≥3	8 (8.2)	8 (8.0)	16 (23.9)	
Intake of drugs (average number)				
Total drugs				
At baseline, mean (SD)	0.54 (0.50)	2.47 (0.50)	5.21 (1.62)	<.001
Cumulative at 24 mo, mean (SD)*	4.0 (2.8)	12.4 (2.0)	25.8 (8.4)	<.001
NSAIDs, mean (SD)				
At baseline, mean (SD)	0.06 (0.24)	0.22 (0.44)	0.25 (0.47)	.006
Cumulative at 24 mo, mean (SD)*	0.29 (0.73)	0.80 (1.4)	1.0 (1.6)	<.001
CKD-EPI$_{cr\text{-}cys}$ eGFR, mean (SD), mL/min/1.73 m^2	85.4 (13.4)	80.7 (14.2)	77.4 (17.4)	.0015

SD, standard deviation.
Data (n = 270 at baseline and n = 226 at 24 mo) are crude means (±SD) or n (%) for baseline tertiles of total drug intake (0–1 drugs, n = 100; 2–3 drugs, n = 102; 4–10 drugs, n = 68), Differences between tertiles of total drug intake at baseline were assessed by using a χ^2 test for categorical variables. For continuous variables, *P* for trend (P_{trend}) across tertiles of total drug intake at baseline was calculated from linear regression models using the median value of the individual tertiles as a continuous variable. *P* values are 2-sided; statistical significance was set at $P < .05$.
*Refers to 226 participants and cumulative tertiles of total drug intake at 24 mo (0–8 drugs, n = 72; 9–17 drugs, n = 71; 18–54 drugs, n = 83).

RAAS blockers. In summary, our results were independent of the inclusion or exclusion of RAAS blockers.

Discussion

In this prospective study observing 270 relatively healthy adults aged 60 and older in 5 clinical visits over a 24-month follow-up, both a higher total number of drugs at baseline and a higher cumulative number of drugs over time were associated with a significantly greater decline in kidney function. This association was independent of age, sex, BMI, treatment groups of the original RCT, prevalence of diabetes, prevalence of hypertension, and baseline kidney function, and further adjustment for the CCI did also not change the results. Notably, among this study sample of older adults with knee osteoarthritis, the cumulative intake of NSAIDs was associated with an about 3 times stronger decline in kidney function than the cumulative intake of an average drug. To our knowledge, our study is the first to prospectively assess the association between cumulative intake of drugs and change in kidney function over time among relatively healthy adults age 60 years and older.

Comparison with Other Studies

Consistent with our findings, a recent longitudinal study of Bolmsjö et al[17] in nursing home residents (mean age 85.0 years) found that the number of drugs taken at baseline was an independent risk factor for a decline in kidney function of >3 mL/min/1.73 m^2 in 1 year. This study, however, did not assess the cumulative intake of drugs over time. Similarly, a recent cross-sectional study by König et al[30] found that the prevalence of polypharmacy (defined as ≥5 drugs daily) was associated with an approximately 50% increased risk for CKD in multivariable-adjusted analysis among adults with a mean age of 68.7 years. Also, in line with these results, another cross-sectional study of 1002 patients (mean age 63.5 years) reported an independent association between polypharmacy (≥5 drugs daily) and CKD risk (odds ratio 3.96).

Our subgroup analysis on regular NSAID intake revealed that a higher cumulative number of NSAIDs was associated with a 3-fold greater decline in kidney function over the 24-month follow-up compared with the cumulative intake of an average drug. Acute kidney injury due to NSAIDs is well established among older adults.[12,13] The 3-times stronger association of the cumulative intake of NSAIDs compared with an average drug in our study supports current guidelines that most older adults are advised not to use NSAIDs for pain control because of the increased cardiovascular, renal, and gastrointestinal risk profile.[31]

Putting our findings in a greater context of health effects among older adults, polypharmacy has been linked to incidence of falls,[32] fractures,[32] delirium,[33] cognitive impairment,[34] and increased mortality.[35] In Switzerland, 3.3% of all hospitalizations are due to adverse drug reactions and 8%–11% of hospitalized patients experienced a relevant adverse drug reaction.[36]

This may in part be explained by drug-drug interactions, which have been found to increase dramatically from 13% when taking 2 drugs up to 82% when taking 7 or more drugs.[37] Moreover, older adults are most vulnerable to drug-drug interactions because of physiological changes that alter the pharmacokinetic and pharmacodynamic with higher age.[38] Further, it has been shown that clinicians may misinterpret a drug adverse reaction as a new medical condition, leading to another drug prescription instead of withdrawing the responsible drug.[39]

Notably, on the other hand, the withdrawal of specific classes of drugs among older adults has been associated with a reduction in falls and improvement in cognitive and psychomotor function when discontinuing psychotropic drugs and benzodiazepines.[40] Moreover, cessation of inappropriate antihypertensive agents has been associated with fewer cardiovascular events and deaths.[41]

Strengths and Weaknesses

Our study has several strengths. Most importantly, our study had a prospective design with 5 repeated measurements over a 24-month follow-up for both the high-quality standardized assessment of drug intake and the complete instrument library to calculate the CKD-EPI_{cr-cys} eGFR. We chose the CKD-EPI_{cr-cys} eGFR, as it has been shown to provide the most exact eGFR for the age group of our study.[7,24–26] Further, we were able to adjust our analyses for important confounders such as age, sex, BMI, prevalence of diabetes, prevalence of hypertension, the CCI, and the baseline value of the eGFR that are known to impact kidney function.

Our study also has limitations. Importantly, although (1) the CCI and incident comorbidities were rather low in our study population, (2) we adjusted for possible confounders including important comorbidities (ie, prevalences of hypertension and diabetes at baseline, which are the most common causes of CKD among older adults[42]), and (3) further adjustment for the CCI did not change our result, we cannot rule out that residual confounding has biased our results, in particular that the prevalence of comorbidities rather than the drug treatment of the comorbidities has impacted the kidney function over time. Moreover, the observational design of our study and the moderate sample size per se do not allow for cause-effect inference or generalization of our results, respectively. However, 5 repeated measurements reduced our measurement error, and the study sample was large enough to investigate the subgroup of seniors taking NSAIDs as a subgroup analysis for a high-risk medication among older adults. Another limitation is that participants with an eGFR <30 mL/min were excluded from the original RCT because of safety reasons. Thus, our results can be considered conservative, as individuals with severe kidney impairment were excluded. Another possible limitation is that, at baseline, we were not able to include a measure of prior kidney function or use of medications. To minimize this concern, we adjusted our analyses for baseline eGFR.

Conclusions and Implications

Our findings show a clinically relevant negative and independent association of polypharmacy with kidney function in relatively healthy older adults. Although age alone may lead to a decline in eGFR by about 0.8 to 1 mL/min/1.73 m^2/year in adults over the age of 40,[6,7,43,44] we demonstrated that among adults aged 60 and older, eGFR may decline further and independently by 0.39 mL/min/1.73 m^2 per drug over 2 years, and 3 times more if the drug is an NSAID (−1.21 mL/min/1.73 m^2). Therefore, our study suggests that for kidney health among adults aged 60 years and older, a careful risk-benefit evaluation for each prescribed drug may be warranted. However, more research, including confirmatory large-scale prospective cohort studies on polypharmacy and kidney function, is needed to confirm our findings (ie, to better determine whether indeed the drug treatment, rather than comorbid illnesses themselves, is responsible for our findings).

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Supplementary Table 1
Disease and Frailty-Related Participant Information Over Time

	Incident Diagnoses/Cases				
	Baseline	6 mo	12 mo	18 mo	24 mo
Baseline* and incident† diagnoses					
Hypertension [n (%)]	118 (43.7)	2 (0.7)	4 (1.6)	3 (1.1)	1 (0.4)
Diabetes [n (%)]	16 (5.9)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)
COPD [n (%)]	5 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CKD [n (%)]	7 (2.6)	3 (1.2)	2 (0.8)	1 (0.4)	0 (0.0)
Rheumatologic disease [n (%)]‡	0 (0.0)	n/a	n/a	n/a	n/a
CVD [n (%)]§	30 (11.1)	3 (1.2)	4 (1.6)	2 (0.8)	3 (1.3)
Incident hospitalization‖					
Total [n (%)]	n/a	25 (9.7)	44 (17.3)	41 (16.9)	32 (14.2)
Due to CVD [n (%)]	n/a	5 (1.9)	6 (2.4)	6 (2.5)	7 (3.1)
Frailty criteria**					
Weight loss [n (%)]††	n/a	12 (4.6)	22 (8.7)	21 (8.6)	20 (8.8)
Weakness [n (%)]‡‡	70 (25.9)	81 (31.3)	75 (29.5)	83 (34.2)	76 (33.6)
Exhaustion [n (%)]§§	7 (2.6)	n/a	1 (0.4)	n/a	2 (0.9)
Slowness [n (%)]‖‖	4 (1.5)	0 (0.0)	4 (1.6)	1 (0.4)	1 (0.4)
Low activity [n (%)]***	85 (31.5)	84 (32.40)	84 (33.1)	84 (34.5)	84 (37.2)
Prevalence of frailty [n (%)]†††	n/a	n/a	2 (0.8)	n/a	1 (0.4)

AE, adverse event; *COPD*, chronic obstructive pulmonary disease; *CVD*, cardiovascular disease; *n/a*, not available due to missing information on single follow-ups, or in the case of frailty because of missing information of single criteria needed to calculate the overall frailty score[1]; *SAE*, serious adverse event.
Data (n = 270 at baseline [ie, 0 mo]; n = 259 at 6 mo; n = 254 at 12 mo; n = 243 at 18 mo, n = 226 at 24 mo) are n (%).

*Baseline diagnoses are based on case report file information at baseline.

†Incident diagnoses are based on AE reporting information over the 24-mo period.

‡Inflammatory arthritis including rheumatoid arthritis was an exclusion criterion of the original trial. Information on diagnosis of incident rheumatologic disease cases was unfortunately unclear to define.

§CVD included myocardial infarction, peripheral cardiovascular disease, cerebrovascular insults, or transient ischemic attack.

‖At baseline, all 270 patients can be considered "hospitalized" due to the unilateral knee replacement. Incident hospitalizations are based on SAE reporting information over the 24-mo period (however, no information on acute intensive care was available). Over the 5 diagnoses considered, only incident CVD cases resulted in hospitalizations.

**Based on Fried et al.[1]

††Weight loss was defined as loss of >2.5 kg/6 mo by direct weight measurement based on Fried et al.[1]

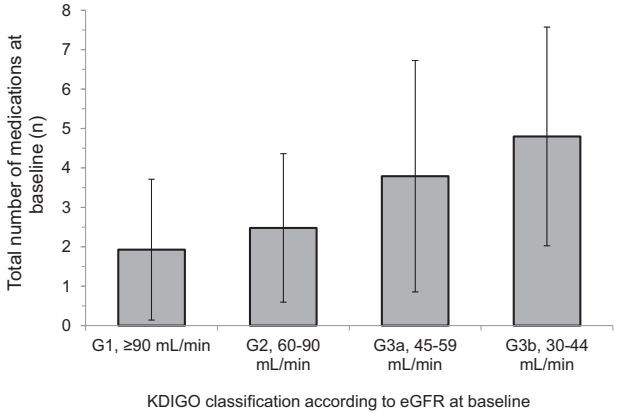
‡‡Weakness was defined by grip strength (measured with by Martin Vigorimeter) based on Fried et al.[1] Cut-points for the weakness criterion at <64.3 kPa (approx. <32.1 kg) for men and <42.7 kPa (approx. <2 kg) for women were used as an approximation of the lowest quintile approach by Fried et al[1] and consistent with a report on optimal cut-points of ≤20 kg (women) and ≤30 kg (men) for the diagnosis of sarcopenia.[2]

§§Similar to Fried et al,[1] exhaustion was operationalized as self-reported negative answer to the question "How often have you been full of energy during the last 4 wk?" from the Short Form (36) Health Survey (SF-36) Questionnaire.[3]

‖‖Similar to the original Fried et al[1] conceptualization, slowness was defined as a gait speed (walking time (s)/4 m) below a certain threshold by gender and height, (ie, ≤0.65 m/s (men ≤173 cm, women ≤159 cm) and ≤0.76 m/s (men >173 cm, women >159 cm).

***Low activity was defined as performing less than 4000 steps per day, equaling the average daily amount of steps of most people perform per day.[4]

†††Prevalence of frailty was calculated based on the overall frailty score of Fried et al.[1]



Supplementary Fig. 1. Total number of drug intake at baseline and kidney function at baseline. Data (n = 270) are the total number of drugs (±SD) taken at baseline categorized by the KDIGO (Kidney Disease: Improving Global Outcomes) classification according to the creatinine and cystatin-based CKD-EPI$_{cr\text{-}cys}$ estimated glomerular filtration rate eGFR at baseline. Participants in the G1 (eGFR > 90, mean eGFR = 97.9), G2 (eGFR 60–89, mean eGFR = 77.7), G3a (eGFR 45–59, mean eGFR = 54.7), and G4b (eGFR 30–44, mean eGFR = 41.0) category had a mean intake of 1.92 (n = 83), 2.48 (n = 163), 3.80 (n = 19), and 4.80 (n = 5) drugs, respectively.

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